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# Applicant Initiated Interview Request Form

Application No.: 10/768,744 First Named Applicant: Christopher A. Hunter
Examiner: Cherie Michelle Woodward Art Unit: 1647 Status of Application: _____

Tentative Participants:
(1) Stacy Landry (2) Christopher A. Hunter
(3) Cherie Michelle Woodward (4) Gary Nickol

Proposed Date of Interview: February 2, 2010 Proposed Time: 12:00 PM (AM/PM)
(Eastern Standard Time)

Type of Interview Requested:
(1) [X] Telephonic (2) [ ] Personal (3) [ ] Video Conference

Exhibit To Be Shown or Demonstrated: [X] YES [ ] NO
If yes, provide brief description: Summary of state of the art at the time of applicants' invention.

## Issues To Be Discussed

| Issues (Rej., Obj., etc) | Claims/ Fig. #s | Prior Art | Discussed | Agreed | Not Agreed |
|---|---|---|---|---|---|
| (1) Priority Claim | All pending | Villarino | [ ] | [ ] | [ ] |
| (2) 102 Rejections | All pending | All cited art | [ ] | [ ] | [ ] |
| (3) State of the art | All pending | Summary attached | [ ] | [ ] | [ ] |
| (4) _____ | _____ | _____ | [ ] | [ ] | [ ] |

[X] Continuation Sheet Attached

Brief Description of Arguments to be Presented:
Please see continuation sheet, which is attached.

An interview was conducted on the above-identified application on _____.
NOTE: This form should be completed by applicant and submitted to the examiner in advance of the interview (see MPEP § 713.01).
This application will not be delayed from issue because of applicant's failure to submit a written record of this interview. Therefore, applicant is advi sed to file a statement of the substan ce of this interview (37 CFR 1.133(b)) as soon as possible.

Applicant/Applicant's Representative Signature — Examiner/SPE Signature

Stacy Landry
Typed/Printed Name of Applicant or Representative

42,779
Registration Number, if applicable

Brief Description of Arguments to be Presented:

(1) Applicants priority document cannot be completely disregarded as a priority document and then be used as extrinsic evidence against Applicants to show the state of the art at the time of the invention.

(2) The cited art does not teach using an IL-27R agonist for immune suppression. The cited art teaches using IL-27R agonists for immune activation. The cited art teaches generally that agonists and antagonists of cytokines can be used to modulate the immune system. It does not teach the particular species claimed.

(3) The state of the art at the time of the invention clearly shows that Applicants invention was, at the time, a novel and surprising use for an IL-27R agonist. In fact, what one of skill in the art at the time of the invention believed was exactly opposite to what is claimed.

Draft Summary of IL-27 Art
To aid in preparation for interview

The following is a narrative that outlines the critical publications that first described the role of the IL-27R (WSX-1/TCCR) in promoting inflammation, the description of IL-27 (composed of p28 and EBI3) and the initial description of the EBI3 KO mice. Also included are references from independent sources that summarize the consensus at various times on the biology of IL-27.

1. The IL-27R (WSX-1) cloned and identified as a type I cytokine receptor and postulated to have a role in the immune system (1).

2. EBI3 cloned (2) , proposed to form a heterodimer with IL-12 p35 (3)(to form what is now known as IL-35) and knocked out(4). Mice were reported to be resistant to oxazolone induced colitis and had reduced production of TH1 (IFN-g) and TH2 (IL-4) cytokines. Also reported that they had a developmental defect in invariant NKT cells – and this was suggested to provide an explanation for the lack of disease as these iNKT cells contribute to this model of oxazalone-induced inflammation. These data provided really the first indication that EBI3 was required for inflammatory responses.

3. The first KO of the IL-27R is reported by a research group from Genentech headed by Fred Desauvage and which contained Nico Ghilardi(5). In this manuscript they presented data that the TCCR (IL-27R) deficient mice had a defect in the ability to produce IFN and consistent with this observation these mice were more susceptible to infection with Listeria. This led the authors to conclude that their "results demonstrate the existence of a new cytokine receptor involved in regulating the adaptive immune response and critical to the generation of a Th1 response".

The apparent specificity of the phenotype described here makes TCCR and its potential ligand candidate targets for therapeutic intervention in Th1-mediated autoimmune disease and allograft rejection.

4. Studies from Hiroki Yoshida in the laboratory of Tak Mak in Toronto were published in Immunity in 2001 and showed that WSX-1 (IL-27R) KO mice were more susceptible to infection with the parasite Leishmania(6). These data were consistent with reduced production of IFN-g in these mice and the authors concluded that "WSX-1 is essential for the initial mounting of Th1 responses"

5. In 2002, studies from the laboratory of Robert Kastelein at DNAX revealed that WSX-1 was a receptor for a novel cytokine composed of p28 and EBI3 which they called IL-27(7). In that manuscript they showed that IL-27 could promote the production of IFN-g from NK and T cells.

6. At this point, a consensus was emerging that IL-27, and signaling through its receptor, was an important step in the generation of Th1 responses. This idea is highlighted in

several reviews that were published at the time by independent experts in the field. For example Robinson and O'Garra (8) concluded that "IL-27 appears to act at an early stage in Th1 development in a manner distinct from IL-12". In that same year, two leading experts in the field of T cell differentiation Ken Murphy and Steve Reiner summarized the state of the field in their review article in Nature Reviews Immunology(9). In that review they have a section devoted to "Recently discovered $T_H1$-cell-promoting factors" and highlight the role of IL-27 in these events and in Figure 8 of that article clearly place IL-27 as a factor that promotes the early differentiation of Th1 cells. Similarly Brombacher and colleagues in a review article concluded that "IL-27 is involved in early Th1 initiation" (10). In 2003 there were three additional publications that reinforced the concept that IL-27 promoted TH1 responses from the groups at Genentech, DNAX and Hiroki Yoshida (11-13). Articles in 2004/2005 (14, 15) continued to highlight the ability of IL-27 to promote the production of IFN-g without mention its anti-inflammatory effects.

7. Based on this literature the blockade of the IL-27R would lead to reduced Th1 responses and that enhanced signaling through the IL-27R would lead to increased Th1 responses. In other words, these studies implicitly implied that neutralization of IL-27 or its receptor would be a viable strategy to prevent or ameliorate pathology caused by Th1 type responses, for instance in the setting of autoimmunity or transplantation. Alternatively, they implied that using IL-27 or promoting signaling through its receptor could be used to augment inflammatory responses; for example during vaccination or cancer therapy.

8. In 2002 we obtained the IL-27R deficient mice from Amgen to determine if the IL-27R was required for the development of protective immunity to the pathogen Toxoplasma gondii. Immunity to this organism is dependent n the ability to produce IFN-g and based on the then existing dogma, we postulated that in the absence of the IL-27R that mice would be unable to mount a protective inflammatory response characterized by the production of IFN-g. Our studies with the IL-27R KO mice demonstrated that, contrary to all expectations, when infected with T. gondii they developed a hyper-inflammatory response characterized by excessive production of IFN-g (and other cytokines) and that the CD4+ T cells in these mice mediated disease. These studies were published in Immunity in late 2003(16) almost a year after the initial patent disclosure. These studies were accompanied by a manuscript from our collaborator, Hiroki Yoshida, that reached a similar conclusion with a different pathogen (17).

9. The finding that the IL-27R was in fact required to dampen inflammatory responses was regarded as extremely novel and was highlighted in an accompanying commentary article(18), by authors associated with Schering Plough/DNAX. In that article they noted that "These data suggest that IL-27 not only is dispensable for the generation of Th1 responses in strongly polarizing conditions, but, likely due to its ability to activate STAT1 and 3, also exerts a powerful negative feedback mechanism that limits T cell hyperactivity and IFN-$\gamma$ production."

10. In contrast to the dogma at the time, the finding that the IL-27R was required to limit immune hyperactivity implied that IL-27 or promoting signaling through the IL-27R would be a useful way to turn off inflammation. Alternatively, the neutralization of IL-27 or blocking signaling through the IL-27R might be a useful way to augment immune responses. These key conclusions are the exact opposite of the conclusions provided in 7 above. Subsequent studies since 2004 have provided ample independent examples of situations where IL-27 is a potent antagonist of inflammatory responses(19-26). Rather than listing all of these examples there are multiple reviews and commentaries that highlight the anti-inflammatory properties of IL-27 and its potential use as a therapeutic to block inflammation (27-35).

11. We do not disagree with the initial conclusion that, under certain circumstances, IL-27 may promote inflammatory responses and there is an established literature on this facet of IL-27 biology. Rather, we would contend that the observation that the IL-27R was actually a potent inhibitor of inflammation was unexpected and would not have been predicted based on the pre-existing literature in 2003.


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